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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/251,570	02/17/1999	JAN G.J. VAN DE WINKEL	MXI-101	3383

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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
DECLOUX, AMY M

ART UNIT	PAPER NUMBER
1644	17

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/251,570	Applicant(s) WINKEL, JAN G.J. VAN DE	
	Examiner Amy M. DeCloux	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-21 are pending.

Claim 7 has been withdrawn from consideration as being drawn to a nonelected invention.

Applicant's amendment filed 10-15-02 (Paper No. 16) is acknowledged and has been entered.

In view of Applicant's amendment, the 112 first enablement rejection has been withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a forcign country, before the invention thereof by the applicant for a patent.

MAINTAINED Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), as evidenced by Graziano et al (J. Immunol. 155:4996-5002, 1995) .

Applicant traverses the rejection on the grounds that as amended the instant claims are drawn to a method of selectively reducing the number or activity of macrophages within a localized area of tissue using two different agents, a first agent which binds to an Fc receptor and a second agent which kills or reduces the activity of the macrophages, and that the referenced teaching by Curnow, does not teach a method which requires two separate and distinct agents. However, the examiner notes that the instant claims do not recite that the recited method encompasses two separate and distinct agents, but encompasses a compound comprising a first agent and a second agent, and nowhere does it say that the first and second agents can not be identical.

Applicant further traverses the rejection on the grounds that with respect to the newly amended claims , Curnow does not teach reducing the number or activity of macrophages within a localized area of tissue, comprising contacting the area of tissue with said compound. However the examiner notes that Stedman's Medical Dictionary 27th Edition defines tissue as: A collection of similar cells and the intercellular substances surrounding them, and that there are four basic tissues in the body: 1) epithelium; 2) connective tissues, including blood, bone, and cartilage; 3) muscle tissue; and 4) nerve tissue. And Janeway (Immunobiology 3rd Edition, 1997, page G:14) teaches that macrophages are migratory cells found in most tissues of the body. Therefore, contrary to applicant's arguments, administration of the mab taught by Curnow into the circulatory system would contact macrophages in a tissue, absent evidence to the contrary.

Therefore, though Applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejection is maintained, essentially for the reasons of record.

MAINTAINED Claims 1-6 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Erickson et al (British Journal of Haematology, 92:718-724, 1996).
Applicant traverses the rejection on the grounds that as amended the instant claims are drawn to a method of selectively reducing the number or activity of macrophages within a localized area of tissue using two different agents, a first agent which binds to an Fc receptor and a second agent which kills or reduces the activity of the macrophages, and that the referenced teaching by Erickson et al., does not teach a method which requires two separate and distinct agents. However, the examiner notes that the instant claims do not recite that the recited method encompasses two separate and distinct agents, but encompasses a compound comprising a first agent and a second agent, and nowhere does it say that the first and second agents can not be identical.

Applicant further traverses the rejection on the grounds that with respect to the newly amended claims, Erickson et al does not teach reducing the number or activity of macrophages within a localized area of tissue, comprising contacting the area of tissue with said compound. However the examiner notes that Stedman's Medical Dictionary 27th Edition defines tissue as: A collection of similar cells and the intercellular substances surrounding them, and that there are four basic tissues in the body: 1) epithelium; 2) connective tissues, including blood, bone, and cartilage; 3) muscle tissue; and 4) nerve tissue. And Janeway (Immunobiology 3rd Edition, 1997, page G:14) teaches that macrophages are migratory cells found in most tissues of the body. Therefore, contrary to applicant's arguments, administration of the mab taught by Erickson et al into the circulatory system would contact macrophages in a tissue, absent evidence to the contrary.

Therefore, though Applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejection is maintained, essentially for the reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

MAINTAINED Claims 1-2, 8-12 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), Graziano et al (J. Immunol. 155:4996-5002, 1995) and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of Uhr et al (U.S. Patent No. 5686072) Ghetie et al (U.S. Patent No. 5578706), Rybak et al (U.S. Patent No. 5840840), Pastan et al (U.S. Patent 5489525), and Bjerke et al (ACTA Derm Venereol (Stockh) 1994; Suppl.186:141-142).

MAINTAINED Claims 1 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), Graziano et al (J. Immunol. 155:4996-5002, 1995), and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of McGrath et al (U.S. Patent No. 5580715), Estis et al (U.S. Patent No. 5026557), Rodwell et al (U.S. Patent 4671958), Lifson et al (U.S. Patent 4869903), and Bagshawe (U.S. Patent 5658568).

Applicant traverses both the rejections on the grounds that the referenced art does not apply to the claims as amended to specify that the recited macrophage-binding compound is administered locally, because said referenced art applies to the treatment of macrophage mediated disorders in the circulatory system as opposed within a localized area of tissue. However the examiner notes that Stedman's Medical Dictionary 27th Edition defines tissue as: A collection of similar cells and the intercellular substances surrounding them, and that there are four basic tissues in the body: 1) epithelium; 2) connective tissues, including blood, bone, and cartilage; 3) muscle tissue; and 4) nerve tissue. And Janeway (Immunobiology 3rd Edition, 1997, page G:14) teaches that macrophages are migratory cells found in most tissues of the body. Therefore, contrary to applicant's arguments, administration of the mab taught by the referenced art into the circulatory system would contact macrophages in a tissue, absent evidence to the contrary.

Therefore, though Applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejections are maintained, essentially for the reasons of record.

NEW GROUNDS OF REJECTION

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Rejection under 35 U.S.C 102(e), Patent Application Publication or Patent to Another with Earlier Filing Date, in view of the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002.

Claims 1-8, 10-13, 15-16 and 18-19 are rejected under 35 U.S.C. 102(e) or (a) as being anticipated by Fanger et al. (US Patent 5,635,600).

Fanger et al teach a method of reducing the number of macrophages by targeting human macrophages for treating diseases including cancer, allergies, infectious and autoimmune diseases by local admistration of a bifunctional antibody (ie a compound comprising a first agent which binds to an Fc receptor derived from monoclonal antibody 22, 32 or 197, and a second agent which kills or reduces the activity of the macrophages (see entire patent, especially columns 5 –7). Therefore, the referenced teachings anticipate the claimed invention.

Claims 1-10,18 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanger et al. (US Patent 5,635,600), Graziano et al (J. Immunol. 155:4996-5002, 1995) and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of Uhr et al (U.S. Patent No. 5686072) Ghetie et al (U.S. Patent No. 5578706), Rybak et al (U.S. Patent No. 5840840), Pastan et al (U.S. Patent 5489525), and Bjerke et al (ACTA Derm Venereol (Stockh) 1994; Suppl.186:141-142).

Erickson et al teach mab197 binds the FcgRI by its fab region to a nonligand binding domain of FcgRI as well as by its fc region and that it can effectively crosslink FcRgI on the surface of the human U-937 human monocyte-like cell line resulting in receptor activation and modulation and that down modulation of FcgRI on circulating monocytes occurs in vivo after infusion of murine mab 197 in ITP patients, (see entire article, especially page 722, second paragraph of the discussion, and last paragraph of page 723). Erickson et al also teaches ITP is characterized by destruction of immunoglobulin coated platelets by mononuclear phagocytes and that macrophages are thought to be the major effectors in platelet destruction in ITP, and that the patient showed major clinical improvement after the first mab infusion (see entire article especially page 718, first paragraph, page 719, first full paragraph, and page 722, column 2, third full paragraph).

Graziano et al teach that mabs 22 and 32 bind the FcgRI receptor with their Fv at sites that are distinct from the Fc binding site, and that the humanization of monoclonal antibody 22 eliminates immunogenicity (see entire article including third paragraph of page 4996) and represents an important step in the development of anti-FcgRI-based molecules for the treatment of human diseases (see entire article including the last paragraph the article).

Erickson et al. teach as above.

Fanger et al. teaches as above.

Uhr et al teach various ricin A chain-containing anti-CD19 and anti-CD22 immunotoxins to be potentially useful reagents for the clinical treatment of human B cell leukemias and lymphomas and the use of modified components in immunotoxin, such as Fab' antibody fragments and deglycosylated ricin A chain (dgA), has also been investigated (see entire patent, especially column 4, lines 39-64).

Ghetie et al also teach the toxin moiety of the immunotoxin may be any one of a variety of toxins that are commonly employed in the art include, for example, gelonin and saporin and ricin A chain, and most preferably, deglycosylated ricin A chain, (see entire patent, especially column 7, lines 21-27).

Rybak et al teach the use of an RNase protein (preferably, a mammalian protein) as a toxic moiety in a directed cytotoxin and that some members of the RNase A superfamily: include onconase. Cytotoxic reagents of the present invention comprise a protein and recognition moiety of specific binding with a chosen cell surface marker, (see entire patent, especially column 7, lines 30-36).

Pastan teaches cytotoxic binding proteins of the invention are produced by fusing a cytotoxic domain and antigen binding domain derived from monoclonal antibodies. A variety of cytotoxic molecules are suitable for use as the cytotoxic domain in the immunotoxins described here including Pseudomonas exotoxin A (PE), (see entire patent, especially column 8, lines 10-25).

Bjerke et al teach that highly active psoriatic lesions showed highest reactivity with FcRgI monoclonal antibodies and the number of FCR positive cells decreased in correlation to the improvement following therapy (see entire article, especially the first paragraph of the Results section and the Abstract)

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have combined the immunotoxin technology taught by Vitetta, Rybak and Pastan which comprises an antibody or antibody fragment thereof that binds to FcgRI as taught by Erickson, Graziano and Fanger linked to a toxin as taught by Vitetta, Rybak and Pastan because said immunotoxin will bind to an FcgRI receptor and kill or reduce the activity of FcRgRI bearing macrophages. Furthermore it would have been obvious to one of skill in the art at the

time the invention was made to have used said immunotoxin in treating or preventing a disease characterized by an aberrant activity or number of macrophages, such as psoriasis or ITP as taught by Bjerke et al and Fanger et al., respectively, since reducing the number and or activity of macrophages in a macrophage mediated disease should be effective treatment. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have used the mabs 22, 32 and 197, since Erickson, Graziano and Fanger teach these monoclonal antibodies can bind the FcgRI at a site which is not bound by an endogenous immunoglobulin, and therefore would not interfere with normal Ig mediated uptake of said macrophages. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have humanized the mabs 22, 32 and 197, since Graziano et al teach that the humanization of the monoclonal antibody 22 reduces or eliminates immunogenicity (and would similarly apply to the humanization of monoclonal antibodies 32 and 97) and is an important step in the development of anti-FcgRI-based molecules for the treatment of human diseases. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have used as the toxin part of the immunotoxin, any one of the toxins Gelonin, Saporin, Exotaxin A, Onconase, and Ricin A, since Vitetta, Rybak and Pastan teach that these toxins would be effective in an immunotoxin.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanger et al. (US Patent 5,635,600), Graziano et al (J. Immunol. 155:4996-5002, 1995), and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of McGrath et al (U.S. Patent No. 5580715), Estis et al (U.S. Patent No. 5026557), Rodwell et al (U.S. Patent 4671958), Lifson et al (U.S. Patent 4869903), and Bagshawe (U.S. Patent 5658568).

McGrath et al teaches the following; a method that features a liposome preparation containing within the liposome macrophage-specific cytotoxin or a broad-spectrum cytotoxic agent for the uptake of the cytotoxin-containing liposome preferentially by a macrophage. Targeting of the cytotoxin-containing liposome to a macrophage provides specificity of delivery and increased uptake. Targeting is accomplished by incorporation or attachment of a macrophage-specific antibody such as anti-CD14 to the liposome. Appropriate lipids and other agents and methods for the preparation of therapeutic liposomes are well known in the art, (see entire patent, especially column 6, lines 66-67 and column 6, lines 1-15).

Estis al teach that liposomes carrying CL2MDP, by referring to the reference Claassen, E. et al., "Immunomodulation with Liposomes: the Immune Response Elicited by Liposomes with Entrapped Dichloromethylene-Diphosphonate and Surface-Associated Antigen or Hapten", Immunol., 60:509-515 (1987), (see entire patent, especially column 1).

Rodwell et al teach liposome mediated delivery of pharmaceutical agents and that whether or not liposomes are coated with antibody molecules, liposomes are readily phagocytosed by macrophages and removed from circulation before reaching other target sites, (see entire patent, especially column 19, lines 35-38).

Liffson et al teach that a protein may be administered in a liposome-encapsulated form, and attached to a carrier, such as an anti-T cell, anti-macrophage, or anti-HIV antibody, for targeting the protein to HIV-injectable or infected cells, (see entire patent, especially column 7, lines 32-37).

Bagshawe teaches the advantages of using antibody fragments, rather than whole antibodies, are several-fold, including the smaller size of the fragments that may lead to improved pharmacological properties, such as better penetration of solid tissue, and effector functions of whole antibodies, such as complement binding, are removed, and Fab, Fv, ScFv antibody fragments can all be expressed in and secreted from E. coli, thus allowing the facile production of large amounts of the said fragments, (see entire patent, especially column 4, lines 1-19).

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have combined the macrophage binding monoclonal antibody compounds taught by Erickson, Graziano and Fanger within a liposome in the claimed method because said compounds bind macrophages as taught by Erickson, Graziano and Fanger and discussed supra, and because Liffson et al teach that a protein may be administered in a liposome-encapsulated form, and antibodies are proteins and because Rodwell et al teaches that liposomes are readily phagocytosed by macrophages. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have used a single chain antibody, or fragment thereof of the FcgRI binding monoclonal antibodies taught by Erickson, Graziano and Fanger since Bagshawe teaches the advantages of using antibody fragments including improved pharmacological properties. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have combined the cytotoxic agent CL2MDP in a liposome in the claimed method because Estis al teach that liposomes can carrying CL2MDP and because McGrath et al teaches a method that features a liposome preparation containing within the liposome macrophage-specific cytotoxin or a broad-spectrum cytotoxic agent for the uptake of the cytotoxin-containing liposome preferentially by a macrophage and that methods for the preparation of therapeutic liposomes are well known in the art .

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 872-9306 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, Ph.D.,
Patent Examiner
February 21, 2003

Patrick Nolan, Ph.D.
Primary Patent Examiner
Group 1640